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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,694	TAGUCHI ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6,7 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6,7 and 11-14* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 4, 6, 7 and 11-14 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 22 December 2008 has been entered.

This Office Action is in response to Applicants' Amendment and Remarks filed on 22 December 2008 in which claim 1-3, 5 and 8-10 were cancelled, claims 4 and 11-13 are amended to change the scope and breadth of the claims, and new claim 14 is added.

Priority

This application is a National Stage entry of PCT/JP03/11669 filed on 1 November 2005 and claims priority to foreign application Japan 2002-265982 filed on 11 September 2002. A certified copy of the foreign priority document in Japanese has been received. No English translation has been provided.

Claim Objections

Claim 12 is objected to because of the following informalities: The term "crosslinking" is spelled incorrectly in the last line of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "includes a moiety derived from the biological low-molecular weight compound" in claim 14 renders the claim herein indefinite. It is unclear which moiety of the biological low-molecular weight compound Applicants are referring to. The moiety as recited in the claims could refer to a carboxyl group, alkyl groups, or even succinimide groups, all of which are constituents of the biological low-molecular weight compound.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 6, 7 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crosslinked high-molecular weight product wherein the high-molecular weight compound is a specific protein, specific glycosaminoglycan, chitosans, specific polyamino acids and specific polyalcohols and a method for using a crosslinked high-molecular weight product wherein the high-molecular weight compound is a specific protein, specific glycosaminoglycan, chitosans, specific polyamino acids and specific polyalcohols, does not reasonably provide enablement for a crosslinked high-molecular weight product wherein the high-molecular weight compound is any protein, any glycosaminoglycan, chitosans, any polyamino acids and any polyalcohols, or a method for using a crosslinked high-molecular weight product wherein the high-molecular weight compound is any protein, any glycosaminoglycan, chitosans, any polyamino acids and any polyalcohols. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or

guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected invention is drawn to a crosslinked high-molecular weight product wherein the high-molecular weight compound is one of proteins, glycosaminoglycans, chitosans, polyamino acids, and polyalcohols. The rejected invention is also drawn to a method for using a crosslinked high-molecular weight product by applying the product as indicated in claims 12 and 13 wherein the high-molecular weight compound is one of proteins, glycosaminoglycans, chitosans, polyamino acids, and polyalcohols.

Relative skill of those in the art: The relative skill of those in the art is high.

Breadth of claims: The claims are extremely broad in that they encompass any protein, glycosaminoglycan, chitosan, polyamino acid, and polyalcohol as the high-molecular weight compound, as well as a method for using any crosslinked high-molecular weight product wherein the crosslinked high-molecular weight compound is any protein, glycosaminoglycan, chitosan, polyamino acid, and polyalcohol.

Furthermore, the recitations, “proteins,” “glycosaminoglycans,” “chitosans,” “polyamino acids,” and “polyalcohols" are seen to be merely functional language. Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does “little more than outline goal appellants hope the

recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405 (emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus…" at 1406 (emphases added).

Thus, Applicant's functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicant's, neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

Amount of guidance/Existence of working examples: The specification only provides working examples for a crosslinked high-molecular weight product wherein the crosslinked high-molecular weight product is collagen, a protein. The specification further indicates that examples of proteins that can be used in preparing the crosslinked product include collagen, atelocollagen, alkali-soluble collagen, gelatin, keratin, serum albumin, egg albumin, hemoglobin, casein, globulin, and fibrinogen; and examples of

glycosaminoglycans that can be used include chondroitin sulfate, dermatan sulfate, hyaluronic acid, heparan sulfate, heparin, and keratan sulfate. The specification also indicates that the type and molecular weight of the polyamino acids and polyalcohols are not limited.

State of the prior art/Predictability or unpredictability of the art: The skilled artisan would view that it is unlikely that one can predict whether all compounds that meet the requirements as disclosed in the instant specification, wherein the high-molecular weight compound is any proteins, glycosaminoglycans, chitosans, polyamino acids, and polyalcohols, could successfully be metabolized *in vivo* after application *in vivo*. For example, prions, which are proteins, are known to be involved in prion diseases associated with Creutzfeldt-Jakob disease ("mad cow"). In this situation, the prion proteins are resistant to degradation. With regards to polyalcohols, in the absence of any limiting definition in the specification, a polyalcohol can be any compound containing multiple alcohol functional groups. A 30-carbon alkyl chain containing six hydroxyl groups would be considered a polyalcohol. However, a skilled artisan would view it unlikely that such a compound, when crosslinked as claimed, could successfully be fully metabolized *in vivo*.

Furthermore, one of ordinary skill in the art would view that it is highly unlikely that a crosslinked high-molecular weight product wherein the high-molecular weight compound is any proteins, glycosaminoglycans, chitosans, polyamino acids, and polyalcohols could be successfully applied to one of biological adhesives, hemostatic agents, materials for embolizing blood vessels, sealing materials for aneurysem,

adhesion preventing agents, scaffolds for tissue regeneration, and as a drug carrier. For example, some proteins, glycosaminoglycans, polyamino acids, and polyalcohols are known to be either toxic or incompatible when used in the environments for the purposes as claimed, i.e. ricin. Thus, it is unlikely that a skilled artisan would use such materials in the preparation of a high-molecular weight product for use in the methods as instantly claimed, particularly since it is highly likely that these compounds would cause adverse effects and likely result in additional problems.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully describe the genus, visualize, or recognize, the identity of the members of the genus by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co*. Hence, in the absence of fully recognizing the identity of the members of the genus herein, one of ordinary skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the claimed product or its use in the instantly claimed methods.

Genetech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, e.g., breadth of claims, the amount of guidance provided and the predictability of the art, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4, 6, 7 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 2000-212286 by Nagura *et al.* (machine translation, of record).

Nagura *et al.* disclose a biodegradable gelatin gel (Section 0002) that is obtained by adding a polycarboxylic acid to gelatin and heating it to introduce chemical crosslinkages. Polycarboxylic acids included in the invention are, but not limited to, malonic acid, fumaric acid, succinic acid, adipic acid, citric acid, tartaric acid and malic acid. Nagura *et al.* further teach that the gel is not limited to crosslinking with gelatin, but also includes water-soluble proteins such as water-soluble polysaccharides (such as

chitosan, alginic acid and chondroitin sulfate) and collagen. Nagura *et al.* disclose that the gelatin gel is considered a biodegradable biomaterial that can be used as an artificial skin, wound dressing material, and a cell culture based material (Section 0008).

It is noted that the Nagura *et al.* do not explicitly indicate that the gelatin gel biomaterial is metabolized *in vivo*. However, since the gelatin gel claimed by Applicant is the same as that disclosed by Nagura *et al.*, and Nagura *et al.* further indicate that the gel is biodegradable, it is inherent that the gelatin gel biomaterial disclosed by Nagura *et al.* can also be metabolized *in vivo*. When, as here, the prior art appears to contain the exact same compound and Applicant's own disclosure supports the suitability of the prior art composition as the inventive compound, the burden is on the Applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicants are requested to note that since claim 4 is directed to a crosslinked high-molecular weight product, that the recitation "obtained by modifying at least one carboxyl group of malic acid, oxalacetic acid, citric acid, or *cis*-aconitic acid with n-hydroxysuccinimide or N-hydroxysulfosuccinimide" is not a determination of patentability, so long as the product is the same. See MPEP § 2113.

The following is a quotation from MPEP § 2113:

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

Thus, the biodegradable gelatin gel obtained by crosslinking a polycarboxylic acid, such as citric acid, with gelatin, disclosed by Nagura *et al.*, anticipates claims 4, 6, 7 and 14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[Section 0001]

Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000-212286 by Nagura *et al.* (of record) as applied to claims 4, 6, 7 and 14 above, and further in view of US Patent No. 6,166,130 to Rhee *et al.* (herein referred to as the '130 patent, of record).

The teachings of Nagura *et al.* were as described above in the claim rejections under 35 USC § 102. Nagura *et al.* do not teach a method for applying the crosslinked high-molecular-weight product as indicated in the claim limitations of claims 12 and 13.

The Rhee '130 patent teaches methods for using crosslinked polymer compositions to affect adhesion between a first surface and a second surface. The crosslinked composition can include proteins such as collagen and derivatives of various naturally occurring polysaccharides, such as glycosylaminoglycans (column 11,

line 38 and claims 11-13). Rhee *et al.* further teach methods for using the crosslinked polymer compositions as bioadhesives (abstract and column 17, line 15) to effect tissue augmentation (abstract and line 16), to inhibit the formation of surgical adhesions (abstract and column 19, line 53), to coat a surface of a synthetic implant (abstract and column 20, line 20), to treat aneurism (column 20, line 53), and to deliver biologically active agents (column 15, line 32).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagura *et al.*, concerning a biodegradable gelatin gel that is obtained by adding a polycarboxylic acid to gelatin and heating it to introduce chemical crosslinkages, with the teachings of the Rhee '130 patent, regarding methods for using crosslinked polymer compositions to effect adhesion between a first surface and a second surface. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Nagura *et al.*, that the obtained polymer gel film is both biodegradable and biocompatible and thus useful for medical applications.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

[Section 0002]

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000-212286 by Nagura *et al.* (of record) in view of Hermanson (chapter 3, entitled "Zero-Length Cross-Linkers", of record).

The teachings of Nagura *et al.* were as described above in the claim rejections under 35 USC § 102.

Nagura *et al.* do not teach polycarboxylic acids that are modified in at least one carboxyl group with N-hydroxysuccinimide or N-hydroxysulfosuccinimide.

Hermanson teaches zero-length crosslinkers that mediate the conjugation of two molecules by forming a bond containing no additional atoms. Zero-length crosslinking agents eliminate the potential for crossreactivity between two substances to be coupled together by mediating a direct linkage between the two substances (p. 169, paragraph 1). Carbodiimides, such as EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), are the most popular type of zero-length crosslinkers in use, being efficient in forming conjugates between two protein molecules, between a peptide and a protein, between oligonucleotides and proteins, or any combination of these with small molecules (p. 169, last paragraph). N-hydroxysulfosuccinimide (sulfo-NHS) are hydrophilic active groups that react rapidly with amines on target molecules (p. 173, first full paragraph). Figure 108 provides a schematic of the reaction (p. 175). In the presence of EDC, sulfo-NHS modifies the carboxylic acid group of a molecule/protein to form a sulfo-NHS activated intermediate. In the presence of amine nucleophiles that can attack at the carbonyl group of the NHS-ester, the sulfo-NHS group rapidly leaves, creating a stable amide linkage with the amine (p. 173, first full paragraph). The advantage of adding sulfo-NHS to EDC reactions is to increase the stability of the active intermediate, which ultimately reacts with the attacking amine (p. 173, second full paragraph). EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase

the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, last paragraph).

A general protocol for the conjugation of a protein to a molecule (i.e. small molecule, peptide, another protein, etc.) is provided (p. 174-176). The protein to be modified is dissolved in 0.1 M sodium phosphate, pH 7.4 at a concentration of 1-10 mg/mL (p. 174, step 1). The molecule to be coupled is also dissolved in 0.1 M sodium phosphate, pH 7.4 (p. 175, step 2) and then added to a solution of the protein in at least a 10-fold molar excess over the amount of protein present (particular important when the conjugation is to a small molecule) (p. 175, step 3). EDC is then added to the protein/molecule solution to obtain a 10-fold molar excess of EDC to the protein (p. 175, step 4). Alternatively, a 0.05-0.1 M EDC concentration would also work well. Sulfo-NHS, at a final concentration of 5 mM, is then added to the reaction (p. 175, step 4) which is allowed to proceed for 2 h at room temperature (p. 176, step 5) before purification of the conjugate by gel filtration or dialysis (p. 176, step 6).

It is noted that the Nagura *et al.* do not explicitly indicate that the gelatin gel biomaterial is metabolized *in vivo*. However, since the gelatin gel claimed by Applicant is the same as that disclosed by Nagura *et al.*, and Nagura *et al.* further indicate that the gel is biodegradable, it is inherent that the gelatin gel biomaterial disclosed by Nagura *et al.* can also be metabolized *in vivo*. When, as here, the prior art appears to contain the exact same compound and Applicant's own disclosure supports the suitability of the prior art composition as the inventive compound, the burden is on the Applicant to show a novel or unobvious difference between the claimed products and the products of the

prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

It is also noted that Hermanson does not explicitly teach the reaction conditions as indicated in the limitations of claim 11. However, it is considered well within the capabilities of one of ordinary skill in the art to optimize the reaction conditions to provide optimal conditions for the conjugation reaction. See below for recitation of section from MPEP § 2144.05. Furthermore, the protocol as disclosed by Hermanson provides for a range of workable conditions.

The following is a recitation from MPEP § 2144.05:

> A. Optimization Within Prior Art Conditions or Through Routine Experimentation
> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagura *et al.*, concerning a biodegradable gelatin gel that is obtained by adding a polycarboxylic acid to gelatin and heating it to introduce chemical crosslinkages, with the teachings of Hermanson, regarding the mediation of the conjugation between a protein and a molecule with sufo-NHS/EDC. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Hermanson, that zero-length crosslinking agents (such as sulfo-NHS and EDC) eliminate the potential for crossreactivity between two substances to be coupled together by mediating a direct linkage between the two substances (p. 169, paragraph 1). Moreover, Hermanson further teaches that

EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase the yield of conjugation over that obtained solely with EDC (p. 173, last paragraph).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 22 December 2008 with respect to the rejection of claims 4, 6, 7 and 11 made under 35 USC § 103(a) as being unpatentable over Nagura *et al.* and Hermanson, have been fully considered but they are not persuasive.

Applicants argue that the Hermanson reference does not meet the claimed limitation of biological low-molecular weight compound as both claim 4 and claim 11 recite "the biological low-molecular weight compound is obtained by modifying at least one carboxyl group of malic acid, oxalacetic acid, citric acid, or *cis*-aconitic acid with N-hydroxysuccinimide or N-hydroxysulfosuccinimide." With regards to claim 4, this argument is not persuasive because, as indicated in the rejection above under 35 USC § 102, claim 4 is directed to a crosslinked high-molecular weight product. Therefore, whether the product is obtained by a starting material wherein the carboxyl groups of the instantly claimed acids are modified or not is not a determination of patentability, so long as the product is the same. See MPEP § 2113.

The following is a quotation from MPEP § 2113:

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

With regards to claim 11, this argument is not persuasive because Nagura *et al.* already teach the instantly claimed crosslinked high-molecular weight product. The teachings of Nagura *et al.* is different from the instantly claimed method because the reference does not teach the method of making the product as instantly claimed. Hermanson is relied on as a secondary reference to teach how and why one would modify a small molecule, such as a polycarboxylic acid, with N-hydroxysuccinimide or N-hydroxysulfosuccinimide, in a coupling reaction. Thus, it is the combined teachings of the prior art that renders the claimed invention *prima facie* obvious. Furthermore, Applicants are requested to note that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's further argue that the disclosure of "small molecules" is not specific for one skilled in the art to render obvious the claimed "biological low-molecular weight compound," particularly because Hermanson specifically teaches crosslinking without any intervening linker or spacer. This argument is not persuasive because, as indicated in the paragraph above, Hermanson is relied upon as a secondary reference to Nagura *et al.*, and thus, Applicants cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, when the combined teachings of Nagura *et al.* and Hermanson are viewed as a whole, the small molecule would be the

polycarboxylic acid, such as citric acid, and the protein would be gelatin. Thus, as per the general protocol disclosed in Hermanson, EDC and sulfo-NHS would react with polycarboxylic acid to form an activated ester, which is then reacted with gelatin to form a product that contains a "zero-length cross-linker." As the polycarboxylic acid has more than one reactive acid in the molecule, each is capable of forming an activated ester with EDC and sulfo-NHS. Thus, although Applicants specifically argue that Hermanson teaches zero-length cross-linkers whereas the instant claims specifically introduce the low-molecular weight compound into the product, it is the methodology of activated esters disclosed by Hermanson that is relied upon. Therefore, as just discussed, using the protocol disclosed by Hermanson, the reaction between a polycarboxylic acid that is converted to an activated ester using EDC/sulfo-NHS and gelatin would result in a product that contains no linkers in between, hence "zero-length cross-linker." However, as polycarboxylic acid contains multiple sites for ester activation, these additional sites would also be reacted with EDC/sulfo-NHS and further with gelatin to give a final product in which gelatin is "crosslinked" to another gelatin molecule via the polycarboxylic acid linkage, which Applicants refer to as an intervening linker.

The rejection is still deemed proper and therefore adhered to.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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